STATE OF THE ART: CONCISE REVIEW

Strategies to Improve Outcomes of Patients with *EGFR*-Mutant Non–Small Cell Lung Cancer: Review of the Literature

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ABSTRACT

Epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKI) monotherapy has been regarded as the standard first-line treatment of advanced non–small cell lung cancer (NSCLC) in patients with sensitive epidermal growth factor receptor gene (*EGFR*) mutations. Acquired resistance is inevitable, however, which presents a challenge in the management of patients with such mutations. Here, we summarize the clinical evidence on treatment strategies for both EGFR TKI–naive and acquired EGFR TKI–resistant NSCLC. We reviewed the published literature and abstracts of oral and poster presentations from international conferences addressing treatment strategies that are in use or in clinical development to improve the survival of patients who are EGFR TKI naive and EGFR TKI resistant. Various strategies have been explored to manage EGFR TKI resistance with the aim of prolonging the survival of patients with *EGFR*-mutant NSCLC. Combination strategies in the first-line treatment have been studied most to improve the benefit from EGFR TKI monotherapy and delay the occurrence of resistance. After failure of EGFR TKI monotherapy, continuation of EGFR TKI therapy combined with chemotherapy, immunotherapy, or targeted agents has been used to overcome the development of resistance. In addition, novel compounds designed to act on specific targets associated with EGFR TKI resistance have been in continued clinical development. Treatment regimens that are superior to EGFR TKI monotherapy in the first-line or to overcome acquired EGFR TKI resistance in patients with NSCLC and *EGFR* mutations still need to be developed. Results of ongoing studies will provide more insight into effective treatment strategies for patients with *EGFR* mutations.

Keywords: Non–small cell lung cancer; Epidermal growth factor receptor tyrosine kinase inhibitor; Acquired resistance; Combination strategy

Introduction

Lung cancer is the most common cancer and remains the leading cause of cancer-related death in men and women worldwide. Approximately 80% to 85% of lung cancers are non–small cell lung cancer (NSCLC). More than half of patients in whom NSCLC has been newly diagnosed have advanced-stage disease at diagnosis, which confers a poor prognosis. Despite advances in chemotherapy, median overall survival (OS) is less than 12 months[1] and the 5-year survival rate is less than 1%.[2]

Epidermal growth factor receptor (*EGFR*), a tyrosine kinase receptor, is one of the landmark targets of NSCLC therapy. Several large clinical studies[3–8] have demonstrated that epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs) are superior to chemotherapy as first-line treatments, showing improved

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Table 1. Phase III Studies of EGFR TKI Monotherapy as First-Line Treatment of Patients with NSCLC and *EGFR* Mutations

Study	Treatment	No. Patients	Median PFS (mo)	Median OS (mo)	RR (%)
IPASS[3]	Gefitinib vs. carboplatin-paclitaxel	132 vs. 129	9.5 vs. 6.3[a,9]	21.6 vs. 21.9[9]	71.2 vs. 47.3[a]
WJTOG3405[4]	Gefitinib vs. cisplatin-docetaxel	86 vs. 86	9.2 vs. 6.3[a]	36 vs. 39[9]	62.1 vs. 32.2[a]
NEJ002[5]	Gefitinib vs. carboplatin-paclitaxel	114 vs. 114	10.8 vs. 5.4[a]	27.7 vs. 26.6[9]	73.7 vs. 30.7[a]
OPTIMAL[6] (CTONG-0802)	Erlotinib vs. gemcitabine-carboplatin	82 vs. 72	13.1 vs. 4.6[a]	22.7 vs. 28.9[9]	83 vs. 36[a]
First-Signal[7]	Gefitinib vs. gemcitabine-cisplatin	26 vs. 16	8.0 vs. 6.3[a]	27.2 vs. 25.6	84.6 vs. 37.5[a]
EURTAC[8]	Erlotinib vs. cisplatin-docetaxel/gemcitabine	86 vs. 87	9.7 vs. 5.2[a]	19.3 vs. 19.5	58 vs. 15
LUX-Lung 3[b,10]	Afatinib vs. cisplatin-pemetrexed	230 vs. 115	11.1 vs. 6.9[a]	31.6 vs. 28.2[11]	56 vs. 23[a]
LUX-Lung 6[c,12]	Afatinib vs. gemcitabine-cisplatin	242 vs. 122	11.0 vs. 5.6[a]	23.6 vs. 23.5[11]	66.9 vs. 23[a]

[a] $p < 0.005$.
[b] PFS and RR results are from an independent review assessment. The results of the investigator review assessment were as follows: PFS = 11.1 vs. 6.7 mo ($p = 0.001$) and RR = 69% vs. 44% ($p = 0.001$).
[c] PFS and RR results are from an independent review assessment. The results of the investigator review assessment were as follows: PFS = 13.7 vs. 5.6 mo ($p < 0.0001$) and RR = 74.4% vs. 31.1% ($p < 0.0001$).
EGFR TKI, epidermal growth factor receptor tyrosine kinase inhibitor; NSCLC, non-small cell lung cancer; PFS, progression-free survival; OS, overall survival; RR, response rate; IPASS, Iressa Pan-Asia Study; WJTOG, West Japan Thoracic Oncology Group; NEJ002, North East Japan 002; First-Signal, First-Line Single-Agent Iressa versus Gemcitabine and Cisplatin Trial in Never-Smokers with Adenocarcinoma of the Lung; EURTAC, European Randomised Trial of Tarceva versus Chemotherapy; OPTIMAL, Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive NSCLC: a multicenter, open-label, randomized, phase 3 study; LUX-Lung 3, Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations; LUX-Lung 6, Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring *EGFR* mutations.

responses and prolonged progression-free survival (PFS) for patients with advanced-stage NSCLC and sensitizing *EGFR* mutations. Therefore, EGFR TKIs have been widely recognized as the preferred initial therapy for patients with activating *EGFR* mutations. Acquired EGFR TKI resistance eventually developed in most such patients and progressed within 12 months, however. Importantly, not all patients with *EGFR* mutations are similarly sensitive to EGFR TKIs.

In this review, we provide an overview of viable treatment strategies for patients with NSCLC and *EGFR* mutations. We also summarize clinical studies of systematic therapy aimed at improving the survival benefit in both EGFR TKI–naive patients and in those with acquired-resistance.

Methods

We searched PubMed, MEDLINE, and clinicaltrials.gov to identify clinical studies that included treatment of patients with NSCLC and *EGFR* mutations. We also searched for relevant abstracts of oral and poster presentations submitted to American Society of Clinical Oncology and European Society for Medical Oncology from 2010 to 2015. The search strategy included medical subject headings or keywords for the concepts EGFR TKI naïveté or EGFR TKI resistance combined with medical subject headings or keywords for NSCLC and *EGFR* mutations. Articles or abstracts published in a language other than English were excluded.

EGFR TKI-Naive Patients

EGFR TKI Monotherapy

The first generation of EGFR TKIs—gefitinib, erlotinib, and icotinib—were designed to reversibly combine with the adenosine triphosphate binding sites and thus block *EGFR*-induced activation of downstream signaling, and they have been extensively investigated in NSCLC. Six randomized controlled phase III trials[3–8] (Table 1) have demonstrated that the first-generation EGFR TKIs significantly improved the response rate (RR) and PFS compared with chemotherapy as first-line treatment of advanced NSCLC harboring *EGFR* mutations. However, OS was not improved, possibly because of treatment crossover at progression. A meta-analysis[13] of the six phase III trials confirmed the efficacy of EGFR TKI therapy as first-line treatment in patients with NSCLC and *EGFR* mutations. When compared with chemotherapy, EGFR TKIs were found to result in significantly better PFS and RR, but not OS.

In contrast to first-generation EGFR TKIs, the second-generation EGFR TKIs such as afatinib or dacomitinib are irreversible inhibitors with greater affinity for the *EGFR* kinase domain, and they also inhibit other members of the EGFR family (human epidermal growth factor receptors 2, 3, and 4).[14] Afatinib was approved as a first-line treatment in patients with NSCLC and sensitizing *EGFR* mutations after demonstrating favorable results in the LUX-Lung 3 and LUX-Lung 6 trials (see Table 1).[10,12] Overall survival was

still not improved in either trial.[11] A meta-analysis[15] that included second-generation EGFR TKI trials confirmed that in patients with *EGFR* mutations, EGFR TKI therapy delayed disease progression compared with chemotherapy.

Whether different EGFR TKIs have different efficacy or toxicity profiles in patients with NSCLC and *EGFR* mutations remains uncertain. A recent meta-analysis[16] indicated that erlotinib, gefitinib, afatinib, and icotinib had equivalent efficacy but different toxicity profiles for patients with NSCLC and *EGFR* mutations. Two prospective head-to-head trials that may address this question are currently ongoing: LUX-Lung 7 (NCT01466660, a randomized phase IIb trial comparing gefitinib with afatinib) and ARCHER 1050 (NCT01774721, a phase III trial comparing gefitinib with dacomitinib).

Molecular Patterns to Predict Response to EGFR TKIs

We already know that patients harboring exon 19 deletions (del19) and L858R substitution in exon 21 usually benefit more from EGFR TKIs than do patients with wild-type mutations.[15] These two patterns account for approximately 90% of all *EGFR*-activating mutations[17] and are regarded as EGFR TKI–sensitizing mutations. However, relatively little is known about other uncommon *EGFR* mutations such as insertion mutations in exon 20, which may be associated with a lack of response to TKIs.[17]

Recently, several reports indicated that the efficacy of EGFR TKIs may differ for del19 and exon 21 L858R mutations. A meta-analysis[18] incorporating all available data from correlative studies confirmed that patients with the del19 mutation were associated with statistically longer PFS than were those with exon 21 L858R *EGFR* mutations. Additionally, superior PFS was found in patients with the *EGFR* del19–positive genotype who received different *EGFR*-targeted agents (gefitinib, erlotinib, or afatinib). Analysis of two phase III trials, LUX-Lung 3 and LUX-Lung 6, indicated that afatinib improved OS for patients with *EGFR* del19 mutations, but not for patients with L858R mutations. These results indicate that patients with *EGFR* del19 and L858R mutations may have differential responses to EGFR TKIs.[11] Several hypotheses have been proposed to explain the higher efficacy of EGFR TKIs in patients with NSCLC and exon 19 deletions than in those with L858R mutations; for example, exon 19 deletions might be more efficiently inhibited by EGFR TKIs than are exon 21 L858R mutations, T790M mutations occur more frequently in exon 21 L858R mutations, or exon 21 L858R mutations coexisting with other uncommon mutations might affect the sensitivity of exon 21 L858R mutations to EGFR TKIs. Nevertheless, the true mechanism remains unclear.[18–20]

In addition to *EGFR* mutation patterns, several other biomarkers have been suggested for identifying patients who are likely to achieve limited responses with EGFR TKIs. One is the gatekeeper T790M point mutation, which increases the affinity of EGFR for adenosine triphosphate and consequently attenuates the binding efficacy of EGFR TKIs.[21] The de novo T790M mutation has been associated with shorter duration of the response to EGFR TKIs and was a negative predictive marker for PFS in patients with NSCLC who were treated with first-line EGFR TKI.[22,23] Another predictive biomarker is BIM (a proapoptotic B-cell CLL/lymphoma 2 [*BCL-2*] family protein), which is pivotal in apoptosis induction by EGFR TKIs in *EGFR*-mutant NSCLC. In the European Randomized Trial of Tarceva versus Chemotherapy (EURTAC), PFS with erlotinib was significantly longer for those patients with high levels of BIM expression than for those with low or intermediate levels (12.9 versus 7.2 months, respectively; $p = 0.0003$).[24]

The lack of sufficient data has impeded determination of the optimal therapeutic strategy for patients with *EGFR* mutations, such as insertion mutations in exon 20, who are initially insensitive to EGFR TKIs. Although personalized therapy may be required to enhance survival, further investigations are needed to develop effective strategies.

Combinations of EGFR TKIs and Chemotherapy

Single-agent EGFR TKI is considered a standard first-line therapy for patients with activating *EGFR* mutations. To further increase survival benefit, combining chemotherapy or targeted drugs with EGFR TKIs has been widely explored. In general, there are three approaches to combination of EGFR TKIs with chemotherapy.

Concurrent Combinations. Before the predictive effect of *EGFR* mutations was validated, four randomized Phase III clinical trials of concurrent combinations of EGFR TKIs and chemotherapy were conducted in unselected populations.[25–28] However, all four trials failed to show a better outcome of the combination than with standard chemotherapy. But whether the combination would improve outcomes in patients with activating *EGFR* mutations was not known. The Cancer and Leukemia Group B 30406 study[29] investigated the combination of paclitaxel/carboplatin and erlotinib versus erlotinib alone in a population enriched for the *EGFR* mutation. No significant differences between treatment groups from the standpoints of PFS, OS, and RR were reported. The efficacy in each treatment arm was greater for patients with *EGFR* mutations than for those without the *EGFR* mutations (Table 2). Because of its small sample size, however, this study lacked sufficient statistical power to determine the efficacy of erlotinib with paclitaxel/carboplatin in patients with *EGFR* mutations.

Table 2. Studies of Combination of EGFR TKIs with Other Agents in Patients with NSCLC and *EGFR* Mutations

Study	Phase	Treatment	Combination Pattern	No. Patients	Median PFS (months)	Median OS (months)	RR (%)
In EGFR TKI-naive patients							
CALGB 30406[29]	II	Erlotinib vs. erlotinib-carboplatin-paclitaxel	Concurrent	33 vs. 33	14.1 vs. 17.2	31.3 vs. 38.1	70 vs. 73
NEJ005[30]	II	Gefitinib-carboplatin/pemetrexed	Concurrent vs. sequentially alternating	41 vs. 39	18.3 vs. 15.3	41.9 vs. 30.7[a,b]	87.8 vs. 84.6
Cheng Y, et al. 2015[31]	II	Gefitinib-pemetrexed vs. gefitinib	Concurrent	126 vs. 65	15.8 vs. 10.9[a]	NR[b]	80.2 vs. 73.8
FASTACT-2[32]	III	Gemcitabine-cisplatin/carboplatin-erlotinib vs. gemcitabine-cisplatin/carboplatin-placebo	Intercalated	49 vs. 48	16.8 vs. 6.9[a]	31.4 vs. 20.6[a]	84 vs. 15[a]
SATURN[33]	III	Erlotinib vs. placebo	Maintenance	307 vs. 311	12.3 weeks vs. 11.1 weeks[a]	12 vs. 11[a]	NA
INFORM[34,35]	III	Gefitinib vs. placebo	Maintenance	15 vs. 15	16.6 vs. 2.8[a]	46.9 vs. 21.0[a]	NA
JO 25567[36]	II	Erlotinib-bevacizumab vs. erlotinib	Concurrent	77 vs. 77	16.0 vs. 9.7[a]	[b]	69 vs. 64
Ichihara E, et al. 2015[37]	II	Gefitinib-bevacizumab	Concurrent	42	14.4 (18.0 vs. 9.4[a,c])	NR[b]	73.8
In patients with acquired EGFR TKI resistance							
IMPRESS[38]	III	Gefitinib-cisplatin/pemetrexed vs. placebo-cisplatin/pemetrexed	Concurrent	133 vs. 132	5.4 vs. 5.4	14.8 vs. 17.2[b]	31.6 vs. 34.1
LUX-Lung 5[39]	III	Afatinib-paclitaxel vs. chemotherapy	Concurrent	134 vs. 68	5.6 vs. 2.8[a]	12.2 vs. 12.2	32.1 vs. 13.2[a]
Janjigian YY, et al. 2011[40]	I/II	Erlotinib-cetuximab	Concurrent	19	3.0	NR[b]	0
Janjigian YY, et al. 2014[41]	Ib	Afatinib-cetuximab	Concurrent	126	4.7 (4.8 vs. 4.6[d])	NA	29 (32 vs. 25[d])

[a] $p \leq 0.05$.
[b] Immature overall survival data/immature at the time of publishing.
[c] Data in patients with exon 19 deletions versus with exon 21 L858R mutations.
[d] Data in T790M-positive versus T790M-negative patients.
EGFR TKI, epidermal growth factor receptor tyrosine kinase inhibitor; NSCLC, non-small cell lung cancer; PFS, progression-free survival; OS, overall survival; RR, response rate; NR, not reached; NA, not available/not assessed.

A phase II study, NEJ005/TCOG0902,[30] compared the concurrent combination of platinum-based chemotherapy and gefitinib with sequentially alternating gefitinib and platinum-based chemotherapy in chemo-naive patients with NSCLC and *EGFR* mutations. Both regimens showed promising efficacy. The median OS for the concurrent regimen was 41.9 months, which was significantly better than that observed in the sequential alternating regimen group ($p = 0.042$) (see Table 2). Another recently reported phase II study comparing gefitinib and pemetrexed with gefitinib alone in East Asian patients with nonsquamous NSCLC and *EGFR* mutations demonstrated that the combination approach led to a significant improvement of nearly 5 months in PFS compared with gefitinib monotherapy (see Table 2).[31] Results of an ongoing phase III study, NEJ009,[42] evaluating gefitinib in combination with carboplatin plus pemetrexed versus gefitinib alone will provide further insight on concurrent chemotherapy in combination with EGFR TKIs as first-line treatment of patients with *EGFR* mutations. (Please note that pemetrexed has not been approved in combination with gefitinib and carboplatin.)

Intercalated Combinations. A potential antagonistic effect of an EGFR TKI plus chemotherapy concurrent combination exists because EGFR TKI induces G1-phase cell cycle arrest that protects cancer cells from the lethal effect of cell cycle phase–dependent chemotherapy, which arrests cells at the mitotic cell cycle phase. In contrast, the intercalated administration of EGFR TKI and chemotherapy has been postulated as a plausible option because it provides temporal separation of these two classes of drugs with conflicting pharmacodynamics.[43]

Intercalated combinations of chemotherapy and EGFR TKIs were explored in two FASTACT randomized trials in unselected patients with advanced NSCLC.[32,44] Significantly improved PFS was reported with intercalated combination in the phase II FASTACT-1 study.[44] In the phase III FASTACT-2 study,[32] patients were randomly assigned to gemcitabine-platinum and intercalated erlotinib for six cycles, followed by erlotinib until progression or to platinum-gemcitabine and placebo for six cycles, followed by erlotinib at progression. The intercalated arm showed significant improvements in PFS and OS,[32] with no differences in toxicity compared with in the chemotherapy plus placebo arm. As expected, significant improvements in PFS and OS were noted only in patients with activating *EGFR* mutations (see Table 2); however, whether the benefit was due to a synergistic effect of intercalated combination of EGFR TKI and chemotherapy or due to maintenance treatment remains unclear. Moreover, the study did not address whether the intercalated combination is more effective than EGFR TKI monotherapy in patients with *EGFR* mutations.

Sequential Combinations with EGFR TKIs as Maintenance Therapy. In clinical practice, *EGFR* mutations are often detected after chemotherapy has already been initiated, a situation for which no consensus recommendation exists. An acceptable approach would be to complete four to six cycles of chemotherapy and then switch to EGFR TKIs as maintenance in patients who did not have progression while receiving chemotherapy. In clinical trials of EGFR TKIs as maintenance therapy following first-line cytotoxic chemotherapy, patients with *EGFR* mutations had longer PFS than did those receiving placebo,[33,34] thus suggesting that the use of EGFR TKIs as maintenance therapy is a plausible option (see Table 2).

Most published studies exploring the combination strategy of EGFR TKI plus chemotherapy have involved a population of nonselected patients with NSCLC and have not focused on patients with *EGFR* mutations. At the time these studies were designed, *EGFR* mutation was not known to be a predictive biomarker. Therefore, the unmet need is to test this combination in patients with activating *EGFR* mutations. Its favorable results compared with those of EGFR TKI alone have already been observed in phase II studies, and ongoing large-scale prospective studies will further validate its effectiveness.

Combinations of EGFR TKIs and Other Targeted Agents

The development of targeted agents such as bevacizumab and cetuximab, which were designed to act specifically either on receptors or ligands that have important roles in tumor biology, has provided new opportunities for treatment of patients with advanced NSCLC. To improve the treatment outcome for patients with *EGFR* mutations, biologically synergistic combinations with EGFR TKIs were extensively explored as various first-line treatment regimens.

Bevacizumab, a recombinant humanized monoclonal antibody, binds to vascular endothelial growth factor A (VEGF-A), causing inhibition of tumor-induced angiogenesis. A phase II study showed that erlotinib and bevacizumab significantly improved PFS compared with erlotinib alone, with an improvement of almost 6 months in patients with NSCLC and *EGFR* mutations (see Table 2). Notably, toxicity led to the discontinuation of bevacizumab in 41% of patients.[36] Another recently published single-arm phase II study of gefitinib plus bevacizumab indicated that median PFS differed significantly between patients with *EGFR* del19 and L858R point mutations (see Table 2).[37] Further investigation of this combination regimen is warranted to validate its efficacy and substantial toxicity. In addition to bevacizumab, ramucirumab, another antiangiogenesis

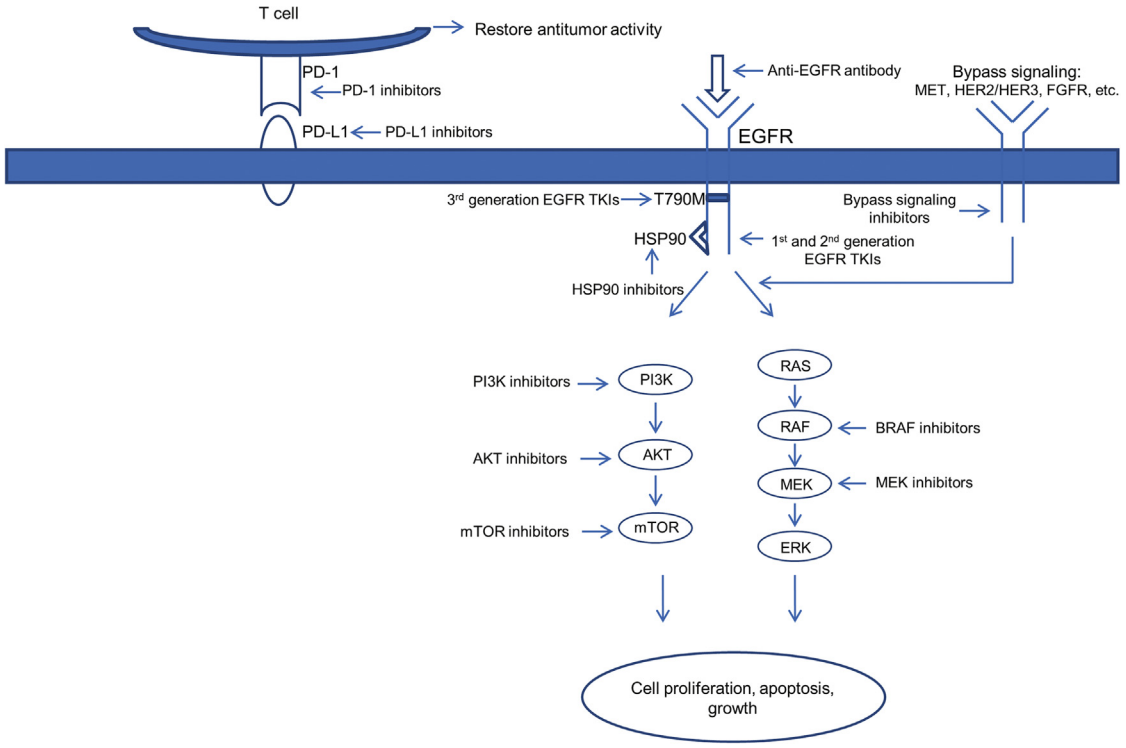

Figure 1. Mechanisms of acquired resistance to EGFR TKIs and agents managing the resistance.

monoclonal antibody targeted against vascular endothelial growth factor receptor 2, is undergoing a phase III clinical trial in combination with erlotinib to evaluate its efficacy and safety in patients with *EGFR* mutations (NCT02411448).

Cetuximab, an EGFR monoclonal antibody, binds to the extracellular domain of *EGFR* and prevents ligand-dependent receptor activation. A preclinical study suggested a synergistic effect of gefitinib and cetuximab, thus supporting combined *EGFR* targeting as a clinically exploitable strategy.[45] An ongoing phase II–III study of cetuximab in combination with afatinib versus afatinib alone in treatment-naive patients with *EGFR* mutations will examine whether afatinib plus cetuximab is better than afatinib alone (SWOG-S1403; NCT02438722).

Patients with Acquired EGFR TKI Resistance

Acquired resistance denotes disease progression after an initial response. Acquired resistance to EGFR TKIs inevitably develops in most patients who experienced significant tumor regressions when treated with the drug. Identification of a T790M mutation in a patient with acquired resistance to gefitinib[20] led to further research aimed at understanding the resistance mechanisms. Several potential mechanisms of resistance to *EGFR* inhibition have been identified (Fig. 1): (1) development of secondary *EGFR* mutations such as the gatekeeper T790M point mutation, which is the most frequently occurring mechanism of resistance[46]; (2) activation of downstream signaling pathways, likely on account of acquired mutations such as mutations in *BRAF* or *PIK3CA*[47]; (3) activation of parallel signaling pathways, including mesenchymal-epithelial transition factor (*MET*), human epidermal receptor 2 (*HER2*), fibroblast growth factor receptor, and AXL, to bypass the inhibited EGFR protein[48–51]; and (4) histologic transformation, specifically epithelial-to-mesenchymal transition or small cell transformation.[52] Clonal heterogeneity also contributes to resistance to EGFR TKIs. Cancer cells evolve by stepwise somatic mutations with sequential subclonal selection (Fig. 2). It is likely that increased resistance to multiple drugs will eventually develop in clones. Tumors in such a state might be rescued by drug combinations.[53] Unfortunately, most studies of investigational drugs or drug combinations in patients with acquired resistance to first-generation EGFR TKI therapy have reported little to no efficacy.

Management According to Progression Patterns

Disease progression in patients receiving EGFR TKI treatment can be generally divided into two patterns: oligo-progression and systemic progression.

In oligo-progression, the primary tumor is controlled and the patient experiences slow, asymptomatic metastasis at a few (usually five or fewer) intracranial or

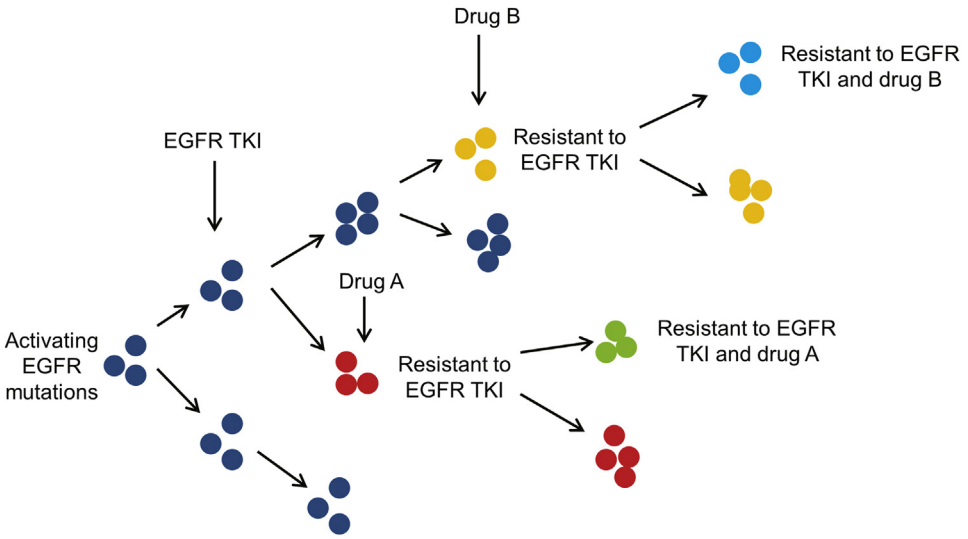

Figure 2. Evolution of cancer cells' clonal heterogeneity in response to drug treatment.

extracranial distant sites. In this condition, local therapy such as stereotactic ablative radiotherapy can be adopted for disease management. Combination of TKIs with local ablation is likely to control the disease, thus resulting in survival benefit.[54–56] For patients with systemic progression, systemic treatment is considered the best choice. In the following sections, we present completed and ongoing efforts to overcome resistance and an algorithm of treatment strategies for patients with systemic progression after an initial response to EGFR TKIs.

Switch to Chemotherapy

Because no successful or reliable therapeutic strategies to overcome EGFR TKI resistance are currently available, switching to chemotherapy remains the most widely accepted approach, with support from current practice guidelines.[57] Because of the complex nature of EGFR TKI resistance, the sensitivity of subsequent chemotherapy may be affected. Two retrospective studies were conducted in an effort to validate this hypothesis but showed inconsistent results.[58,59] A recently reported retrospective cohort study found that pemetrexed single-agent therapy provided significantly longer PFS than did platinum-based doublet chemotherapy for patients with NSCLC and *EGFR* mutations who failed first-line therapy with EGFR TKIs.[60] Prospective randomized studies are needed to provide a definitive recommendation regarding the therapeutic strategy of chemotherapy for this population.

Continuation of EGFR TKIs

Discontinuation of TKIs might lead to rapid disease progression.[61] It is plausible to continue treatment with an EGFR TKI beyond disease progression. In practice, disease management usually depends on clinical factors such as symptoms and tumor burden. Some asymptomatic patients with progression continue to obtain clinical benefit from EGFR TKI treatment and can delay switching to chemotherapy.[62] In addition to continuing treatment with initially effective EGFR TKIs, combinations with chemotherapy or other targeted agents have been explored or are under investigation.

Continuation of Single-Agent EGFR TKI Beyond Progression. The single-arm phase II study ASPIRATION[63] showed that continuation of erlotinib beyond disease progression is a feasible treatment option. The difference between the time-to-response evaluation criteria in solid tumors progression or death and the time to off-erlotinib progression if erlotinib was extended beyond the response evaluation criteria in solid tumors progression was 3.7 months in those patients whose disease progressed after erlotinib. However, randomized studies are needed to further validate the effect of continuation of EGFR TKIs and identify the optimal subsets of patients with *EGFR* mutations who can benefit from post-progression treatment with EGFR TKI.[63]

Continuation of EGFR TKIs and Chemotherapy. Given the potential heterogeneity of EGFR TKI resistance in cancer cells, it is assumed that continuation of EGFR TKI therapy acts on cells remaining sensitive to this agent, whereas chemotherapy acts on the cells resistant to the EGFR TKI.[64]

The phase III IMPRESS study[38] compared continued gefitinib in combination with cisplatin and pemetrexed with cisplatin and pemetrexed in patients with *EGFR* mutations. Unfortunately, the combination including gefitinib failed to prolong PFS and had a deleterious

effect on OS compared with that of chemotherapy alone (see Table 2). Considering the complicated mechanism of resistance to TKI, the study results indicate that personalized treatment is required to overcome such resistance, and future studies should be considered to identify the subsets of patients who could benefit from this combination strategy.

A phase III trial (LUX-Lung 5) compared afatinib and paclitaxel to the investigator's choice of chemotherapy alone in patients who progressed while receiving erlotinib/gefitinib and afatinib. The combination regimen significantly improved PFS and RR compared with chemotherapy alone; OS was similar in both arms (see Table 2).[39]

Several ongoing prospective studies may provide a definitive recommendation about the combination of chemotherapy and erlotinib (NCT01928160, NCT02064491, and NCT02098954) in patients with EGFR TKI–acquired resistance.

Continuation of EGFR TKIs and Other Targeted Agents. The prospect of targeting two different pathways simultaneously, possibly leading to disease control in patients with EGFR TKI resistance, is appealing.

Cetuximab has been used predominantly in combination with EGFR TKIs against drug-resistant tumors. Encouraging preclinical data showed that the combination of cetuximab with afatinib induced tumor regression in erlotinib resistant tumors by decreasing the phosphorylation of total EGFR resulting in inhibition of its signaling.[65] On the basis of these data, a phase Ib study evaluated the combination of afatinib and cetuximab in 126 patients with NSCLC who had progressed during treatment with erlotinib/gefitinib. The combination demonstrated an overall response rate (ORR) of 29% and PFS of 4.7 months. Patients with T790M-positive and T790M-negative mutations had a similar PFS (see Table 2).[41] Whether this dual EGFR blockade strategy is generally efficacious with any EGFR TKI in combination with cetuximab should be clarified in future studies. In a phase I–II study of erlotinib plus cetuximab in patients with resistance to erlotinib, no responses were seen.[40]

EGFR TKI Rechallenge After a Drug Holiday

Another strategy to regain sensitivity to EGFR TKI is to rechallenge with the same or a different TKI after progression of disease in patients receiving a TKI initially and undergoing subsequent chemotherapy. A possible explanation for the clinical benefit of an EGFR TKI rechallenge is that some cytotoxic agents have been reported to restore the sensitivity of NSCLC cells to EGFR TKIs by increasing *EGFR* phosphorylation.[66] It is also possible that chemotherapy during the EGFR TKI–free interval, which is equivalent to a drug holiday for TKI, could decrease the number of EGFR TKI–resistant tumor cells. In a single-arm prospective phase II trial, 23 patients who had previously been controlled (showed response or disease stabilization) with initial gefitinib treatment for at least 3 months and progressed while undergoing subsequent chemotherapy were recruited. Partial response and disease control rate were observed in 21.7% and 65.2% of the patients who were retreated with gefitinib, respectively.[67] Another phase II study evaluating the clinical effects of gefitinib rechallenge in patients with *EGFR* mutations is ongoing (NVALT16, NCT02025218).

Second- and Third-Generation EGFR TKIs

Although afatinib is the most promising second-generation EGFR TKI and has proven to be successful in the first-line setting, its activity against acquired resistance in two phase II studies (LUX-Lung 1 and LUX-Lung 4) was modest.[68,69] Other second-generation TKIs, such as dacomitinib and neratinib, have also been tested against acquired resistance, but limited efficacy has been observed.[70,71]

Third-generation EGFR TKIs specifically designed to overcome T790M mutation are currently being developed. Although only phase I clinical study results have been presented, the activity of the third-generation EGFR TKIs against the T790M mutation has been demonstrated to be impressively promising. The ORR for AZD-9291 (80 mg daily) was 66% with a PFS of 10.9 months in patients with T790M mutations.[72] CO-1686 (500 mg twice daily) showed an ORR of 60% and 57% in heavily pretreated patients harboring the T790M mutation in tissue and plasma testing, respectively.[73] Similarly, HM61713 resulted in a 54.8% ORR with a 95.2% disease control rate in patients with T790M mutations.[74] The safety profile of these third-generation TKIs differs from that of first- or second-generation TKIs and is associated with less frequent and less severe gastrointestinal and skin toxicity. One possible explanation is that these agents are highly selective with less effect on normal cells with wild-type *EGFR* mutations than on first- or second-generation TKIs. The promising efficacy and mild toxicity of AZD-9291 and CO-1686 will be validated in large prospective studies: AURA3 (NCT02151981) and TIGER3 (NCT02322281), respectively.

In treatment-naive patients with NSCLC and *EGFR* mutations, AZD-9291 also showed encouraging results from a recently reported phase I study (ORR 70%, 6-month PFS rate 87%).[75] Phase III studies of AZD-9291 (FLAURA, NCT02296125) and CO-1686 (TIGER 1, NCT02186301) in treatment-naive patients with NSCLC and *EGFR* mutations are ongoing for head-to-

Table 3. Part of Ongoing Studies of Targeted Agents Developed to Overcome EGFR TKI Resistance

Targeted Agent	Treatment Arms	Phase	ClinicalTrials.gov Identifier
cMET inhibitors			
Tivantinib (ARQ197)	Tivantinib + erlotinib	II	NCT01580735
Cabozantinib (XL184)	Cabozantinib + erlotinib	II	NCT01866410
Cabozantinib (XL184)	Cabozantinib	II	NCT02132598
Volitinib (AZD6094)	Volitinib + gefitinib	I	NCT02374645
INC280	INC280 + EGF816	I and II	NCT02335944
INC280	INC280 + gefitinib	II	NCT01610336
PI3K/AKT/mTOR inhibitors			
NVP-BKM120	BKM120 + gefitinib	I	NCT01570296
NVP-BKM120	BKM120 + erlotinib	II	NCT01487265
MK-2206	MK2206 + gefitinib	I	NCT01147211
MK-2206	MK2206 + erlotinib	II	NCT01294306
MAPK inhibitors			
Selumetinib (AZD6244)	Selumetinib + vandetanib	I	NCT01586624
Selumetinib (AZD6244)	AZD9291 + selumetinib vs. AZD9291 + AZD6094 (volitinib) vs. AZD9291 + MEDI4736	I	NCT02143466
Selumetinib (AZD6244)	Selumetinib + gefitinib	I and II	NCT02025114
Selumetinib (AZD6244)	Erlotinib vs. erlotinib + MK-2206 vs. selumetinib + MK-2206 vs. sorafenib	II	NCT01248247
HSP90 inhibitors			
NVP-AUY922 (VER52296)	AUY922 vs. pemetrexed/docetaxel	II	NCT01646125
NVP-AUY922 (VER52296)	AUY922	II	NCT01854034
SNX-5422	SNX-5422	I	NCT01851096
Ganetespib (STA9090)	Ganetespib + ziv-aflibercept	I	NCT02192541

AKT, Ak murine thymoma viral oncogene; MET, mesenchymal epithelial transition factor; PI3K, phosphatidylinositide 3-kinases; mTOR, mammalian target of rapamycin; MAPK, mitogen-activated protein kinase; HSP90, heat shock protein 90.

head comparison with gefitinib or erlotinib from the standpoints of efficacy and tolerability.[76,77] Additional data obtained in the future will help determine the optimal strategy for using third-generation EGFR TKIs in patients with NSCLC and *EGFR* mutations: whether to use them as first-line therapy or after failure of first-generation TKIs.

Treatment Strategies Targeting Alternate Pathways

The third-generation EGFR TKIs specifically targeting the T790M mutation elicited responses in early clinical studies, but most of the other agents targeting alternate pathways contributing to TKI resistance produced modest clinical benefit. For example, *MET* amplification is the second most common mechanism of acquired resistance to EGFR TKIs after T790M point mutation, and targeting *MET* to overcome resistance is a viable option from biologic standpoint. In a phase II clinical study, the *MET* inhibitor cabozantinib administered in combination with erlotinib to patients who had *EGFR* mutations and progressed with an EGFR TKI resulted in an ORR of 8.1% and PFS of 3.7 months, thus warranting further clinical investigation.[78] Treatment with another *MET* inhibitor, INC280, in combination with gefitinib in patients with *EGFR*-mutated and *MET*-positive NSCLC resulted in an ORR of 17%.[79] Another newly emerged agent is heat shock protein 90 (HSP90) inhibitor. The HSP90 is a molecular chaperone that is responsible for the conformational maturation and stabilization of its substrate proteins, including EGFR. AUY922, an HSP90 inhibitor showed single-agent clinical activity in patients with NSCLC and *EGFR* mutations who had progressed just after EGFR TKI therapy with a median PFS rate of 45% at 18 weeks.[80] However, a phase II study of AUY922 and erlotinib in patients with *EGFR*-mutant lung cancer with acquired resistance did not meet its primary end point (ORR 16%).[81] Other compounds targeting alternate pathways, such as *HER2/HER3* inhibitors, phosphoinositide 3-kinase/Ak murine thymoma viral oncogene/mammalian target of rapamycin (PI3K/AKT/mTOR) inhibitors, and mitogen-activated protein kinase inhibitors, are in various stages of clinical development (Table 3). More encouraging results from these trials are expected in the near future.

Immunotherapy

Another potential strategy is the use of immune checkpoint inhibitors such as programmed death (PD)-1 pathway inhibitors, which have drawn much

attention in recent years. Preclinical studies demonstrated that mutant *EGFR* signaling drives expression of programmed death-ligand 1 (PD-L1) and that blockade of the PD-1 receptor improved survival of mice with *EGFR*-mutant tumors.[82] Preliminary results of a study investigating the combination of nivolumab (anti-PD-1 monoclonal antibody) and erlotinib reported an ORR of 19% (four of 21 patients, with three of four responders having previously progressed while receiving erlotinib).[83] Nivolumab has been recently approved by the FDA for the treatment of patients with squamous NSCLC after failure of chemotherapy. Further investigations of nivolumab as monotherapy or in combination with EGFR TKI in patients with NSCLC and *EGFR* mutations will provide further insight into the role of immunotherapy (NCT02323126).

Conclusions and Future Perspectives

EGFR TKI monotherapy has been regarded as the standard first-line therapy for patients with NSCLC and *EGFR*-sensitive mutations. To maximize the survival benefit from first-line treatment in patients with NSCLC and *EGFR* mutations and delay the occurrence of resistance, EGFR TKI-based combination therapy is a reasonable strategy that has been explored using various approaches. The combination of EGFR TKI with chemotherapy or the antiangiogenesis monoclonal antibody has achieved encouraging efficacy, which is to be validated in future large-scale studies. Despite the success of EGFR TKIs as front-line treatment, resistance to these drugs is inevitable and creates a significant challenge in the management of patients with *EGFR* mutations. The heterogeneity of tumors and the complicated mechanisms involved in EGFR TKI resistance have impeded the development of successful solutions for overcoming this resistance. One possible solution is a combination strategy, including combinations of EGFR inhibitors with chemotherapy, immunotherapy, or various targeted agents. Few conclusive studies with encouraging results have been reported to date, thus indicating the need for further investigations—especially of EGFR TKIs in combination with chemotherapy. To obtain meaningful results, careful selection of patients and design of randomized clinical trials should be considered. Novel compounds designed to act on a specific target associated with EGFR TKI resistance have been under continued clinical development. In this regard, the third-generation EGFR TKIs designed to specifically target T790M mutations may lead to a dramatic change in the treatment paradigm for patients with *EGFR* mutations within the next few years. As more data become available in the future, we can expect the development of novel drugs with demonstrated efficiency in overcoming resistance to EGFR TKIs.

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